

**ETS AND  
LUNG CANCER IN NONSMOKERS**

**VOLUME II**

2061690953

## CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer.

### Strength of the association

- Wynder and Kabat wrote in 1990:

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.

Such a weak association calls for special attention to possible sources of bias and confounding.

### Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."<sup>2</sup>
- Exposure indices and risk estimates based on this type of information may be improper and incorrect.
- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when

2061690954

the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

#### Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.<sup>2</sup>

#### Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.<sup>3</sup>

#### Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

### Use of questionnaires

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.<sup>4</sup> Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.
- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.<sup>5</sup>

### Histology

- Lung cancer diagnoses were not always histologically or pathologically verified.<sup>1</sup>
- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).<sup>1</sup>

### "Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.<sup>1</sup> (This is sometimes called "data-dredging.")

### Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."
- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.<sup>6</sup>

### Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a recent scientific symposium in Argentina:

The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological

plausibility can be judged controversially.<sup>7</sup>

The eminent statistician Nathan Mantel concluded the following:

[I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statements, are found at Tabs 1-7.

### CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.<sup>8-21</sup> They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.<sup>8</sup> When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.
- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.<sup>9-12</sup> When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.
- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.<sup>8</sup>
- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.<sup>13-15</sup>

- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable<sup>8</sup>; autopsy or histology results were available for only 11.5% (23 of 200) of the cases<sup>8,16</sup>; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable<sup>8,12</sup>; many possible confounding factors were overlooked.<sup>8,17</sup>

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.<sup>18</sup> In addition, Hirayama has not made his original data available for review.<sup>8,19,20</sup>

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-20. They are highlighted in yellow for useful information and in blue for adverse statements.

## CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.<sup>22</sup> Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).
- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.<sup>8,24</sup> According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."<sup>23</sup>

Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements are found at Tabs 21-23.

REFERENCES  
General Criticisms

1. Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.
2. Kilpatrick, S.J., "Misclassification of Environmental Tobacco Smoke Exposure: Its Potential Influence of Studies of Environmental Tobacco Smoke and Lung Cancer," Toxicology Letters 35: 163-168, 1987.
3. Mantel, N., "Lung Cancer and Passive Smoking," British Medical Journal 294: 440, 1987.  
Newcombe, R., "Towards a Reduction in Publication Bias," British Medical Journal 295: 656-659, 1987.
4. Coultas, D.B., Peake, G.T. and Samet, J.M., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," American Journal of Epidemiology 130(2): 338-347, 1989.  
Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American Journal of Public Health 80(8): 988-990, 1990.
5. Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," American Review of Respiratory Disease 142: 602-606, 1990.
6. Lee, P.N., "Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 25-36.
7. Überla, K., "Epidemiology: Its Scope and Limitations for Indoor Air Quality," Indoor Air Quality (Buenos Aires: National Academy of Sciences of Buenos Aires, Argentina, 1988): 45-60.

REFERENCES  
Criticisms of Hirayama, 1981

8. Überla, K. and Ahlborn, W., "Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 333-340.
9. MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 915-916, 1981.  
MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465, 1981.
10. Lee, P., "Passive Smoking," Food Chemistry and Toxicology 20: 223-229, 1982.
11. Kilpatrick, S. and Viren, J., "Age as a Modifying Factor in the Association Between Lung Cancer in Non-Smoking Women and Their Husbands' Smoking Status," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 195-202.
12. Kilpatrick, S., "An Example of Extra-Poisson Variation Suggesting an Under-Specified Model," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 83-90.  
Kilpatrick, S., "Model Specification Effects in ETS/Nutrition Research," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 257-271.
13. Lee, P., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465-1466, 1981.
14. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1466, 1981.
15. Layard, M. and Viren, J., "Assessing the Validity of a Japanese Cohort Study," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 177-180.
16. Grundmann, E., Miller, K.-M. and Winter, K.D., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

17. Sterling, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.
18. Hirayama, T., Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan, (Basel: Karger, 1990).
19. Adlkofer, F., "Probleme mit dem Passivrauchen (The Problems of Passive Smoking)," Der Kassenarzt 27(51/52): 29-39, 1987. Translation.
20. Ahlbom, W. and Überla, K., "Passive Smoking and Lung Cancer: Reanalyses of Hirayama's Data," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 169-178.
21. Aviado, D., "Toxicological Basis for Regulation of Indoor Air Quality," Journal of Applied Toxicology 8(3): 155-157, 1988.  
Diamond, G. and Forrester, J., "Clinical Trials and Statistical Verdicts: Probable Grounds for Appeal," Annals of Internal Medicine 98(3): 385-394, 1983.  
Gostomzyk, G., "Krank durch Passivrauchen (Disease Due to Passive Smoking?),," Munch med Wschr 124(4):16, 1982. Translation.  
Kornegay, H. and Kastenbaum, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914, 1981.  
Mantel, N., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914-915, 1981.  
Mantel, N., "Epidemiologic Investigations: Care in Conduct, Care in Analysis, and Care in Reporting," Journal of Cancer Research and Clinical Oncology 105: 113-116, 1983.  
Rutsch, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 985, 1981.

REFERENCES  
Criticisms of Trichopoulos, et al., 1981

22. Letzel, H. and K. Überla, "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.
23. Überla, K., "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?," International Archives of Occupational and Environmental Health 59: 421-437, 1987.
24. Heller, W.-D., "Lung Cancer and Passive Smoking," The Lancet II: 1309, 1983.

2061690966